REMARKS

A check for $55 for a one-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Applicant notes that claims 18-22, 40 and 41 are allowable. The Office Action indicates that claims 35-39 would be allowable if they were amended to be dependent on an allowable base claim. Claims 35-39 are not amended herein, however, pending consideration of the remarks below. Claims 17 and 18 are amended herein to correct inadvertent grammatical errors.

Rejection of claims 17, 31 and 33 under 35 U.S.C. §102(b)

The Office Action alleges that claims 17, 31 and 33 are anticipated by Nolan *et al.* In particular, it is alleged that that Nolan *et al.* discloses a method and apparatus that employs fluorescence activated cell sorting (FACS) to verify the delivery of at least one chromosome into a host cell. It is further alleged that the chromosomes disclosed by Nolan *et al.* are 1-10 megabases and thus "large nucleic acids." The Office Action also alleges that the method described by Nolan *et al.* indicates that it is preferential to use chromosomes that are fluorescently labeled that are then detected by fluorimetry. It is alleged that Nolan *et al.* discloses detecting the number of cells that are fluorescent after FACS sorting. It also is alleged that the methods described by Nolan *et al.* include host cells such as fibroblasts and parenchyma stem cells.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and

Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Claim 17 is directed to a method for monitoring the delivery of a large nucleic acid molecule into a cell. The method includes the steps of (a) labeling the large nucleic acid molecule; (b) delivering the labeled large nucleic acid molecule into a cell; and (c) detecting the labeled large nucleic acid molecule in the cell by flow cytometry, fluorimetry, cell imaging or fluorescence spectroscopy, as an indication of delivery of nucleic acid molecule into the cells. Dependent claims further specify cell types and an additional step of (d) determining the number of cells containing the label.

Analysis

Differences between the disclosure of Nolan *et al.* and the rejected claims

Nolan *et al.* describes a method and apparatus for subjecting a cell to a laser light pulse to create a hole in the plasma membrane and introducing a chromosome into the cell. Nolan *et al.* describes the use of FACS to verify chromosome insertion into the cell.

Nolan *et al.* does not disclose delivering labeled large nucleic acid molecules of any size into a cell. Nolan *et al.* states that one method of verifying insertion of a chromosome into a cell is (1) identification of the inserted chromosome using chromomycin A3 and Hoechst 33258, which are known dyes for staining chromosomes in cells; and (2) FACS

sorting of the stained chromosomes. Thus, for example, at page 9, line 25 to page 10, line 6, Nolan *et al.* states:

> There are numerous means for **determining the successful incorporation of a single chromosome into the cell.** It is presently preferred that the verification be made by a FACS machine. Presently, it is preferred that the chromosome be fluorescently labeled. Thus, after insertion of the chromosome, the cell can pass into a recovery chamber where its fluorescent scatter properties are analyzed by the FACS to determine whether one and only one chromosome has been inserted. Current artificial chromosomes are very AT rich due to the fact that they contain a large percentage of pericentric alpha satellite DNA, which is very AT rich. **This type of chromosome is identified and sorted by using chromomycin A3 and Hoechst 33258 stains and dual laser high speed flow cytometry.** The AT rich chromosomes carry a specific ratio of the dyes and can be identified in this manner. (emphasis added)

The above is the only method involving fluorescent detection that is disclosed by Nolan *et al.* The method involves staining the chromosomes using the known dyes chromomycin A3 and Hoechst 33258 *after* the chromosome is introduced into the cell. Hence, Nolan *et al.* discloses fluorescent labeling *after* the chromosome is delivered into a cell, as a means of verifying that the chromosome has been incorporated into the cell.

In contrast, the instantly claimed methods recite labeling a large nucleic acid molecule and delivering the labeled large nucleic acid molecule into a cell. For delivering labeled large nucleic acid molecules into a cell, the nucleic acid molecule must be labeled *prior* to the delivery step. As discussed above, there is no disclosure by Nolan *et al.* of labeling large nucleic acid molecules *prior* to delivery into a cell, nor delivery of labeled nucleic acid molecules into a cell. Therefore, since anticipation requires the disclosure of every element of the claims, Nolan *et al.*, which does not disclose delivering a labeled large nucleic acid molecule into a cell (step (b) of independent Claim 17) , does not anticipate Claim 17, nor Claims 31 and 33, dependent thereon.

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In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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